NHS England

Evidence review: Sapropterin for phenylketonuria

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The content of this evidence review was up-to-date in September 2018. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points

Regulatory status: Sapropterin received a marketing authorisation in 2008 and was launched in the UK in 2009. Sapropterin is licensed for the treatment of hyperphenylalaninaemia in adults, young people and children of all ages with phenylketonuria (PKU) who have been shown to be responsive to treatment with sapropterin.

Sapropterin is also licensed for the treatment of hyperphenylalaninaemia in adults, young people and children of all ages with tetrahydrobiopterin (BH4) deficiency, although use for this indication is outside of the scope of this evidence review.

Sapropterin has an orphan designation. Orphan medicines are:

- used to treat life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the European Union, or
- medicines which, for economic reasons, would be unlikely to be developed without incentives.

Overview

This evidence summary considers the best available evidence for sapropterin for the management of PKU.

PKU is an inherited disease in which deficiency of the enzyme phenylalanine hydroxylase results in raised phenylalanine levels in the blood, causing brain damage, growth failure, behavioural problems and other developmental issues.

The European guidelines on the management of PKU were published in 2017. The guidelines recommend that children aged less than 12 years should maintain a blood phenylalanine level between 120 and 360 micromol/litre, and people aged 12 and over between 120 and 600 micromol/litre.

Sapropterin is a synthetic version of tetrahydrobiopterin, a naturally occurring co-factor for the enzyme phenylalanine hydroxylase. Only people with PKU who have residual phenylalanine hydroxylase activity will respond to treatment with sapropterin. It is essential that response to treatment is assessed, and sapropterin only continued in people whose phenylalanine concentration reduces by an appropriate amount.

This evidence review focuses on 3 double-blind randomised controlled trials (RCTs, Levy et al. 2007, Trefz et al. 2009, Burton et al. 2015) and an open-label RCT (Muntau et al. 2017). Additional information is provided by 2 extension studies (Lee et al. 2008, Burton et al. 2011) and 5 observational studies (Longo et al. 2015, Aldámiz-Echevarría et al. 2015, Aldámiz-Echevarría et al. 2013, Feldmann et al. 2017, Cazzorla et al. 2014).

Overall, the results of these studies suggest that sapropterin reduces blood phenylalanine concentrations and increases phenylalanine tolerance in adults and children with PKU, allowing people to increase the natural protein in their diet. The impact of sapropterin on development and day-to-day living is less clear, although these outcomes were reported in

fewer studies, often of lower quality. Adverse events, while relatively common were generally mild to moderate in severity and rarely resulted in treatment being stopped.

Levy et al. 2007 and Lee et al. 2008 found that people with PKU not adhering to a phenylalanine-restricted diet who were treated with sapropterin for up to 22 weeks had a statistically significant reduction in blood phenylalanine concentrations of approximately 200 micromol/litre from baseline (approximately 25% relative reduction). This reduction is significantly higher than that seen in people not treated with sapropterin who continued their current diet, whose phenylalanine levels remained constant. In Trefz et al. 2009, children whose phenylalanine levels were well controlled using a restricted diet had significantly lower phenylalanine concentrations after 3 weeks treatment with sapropterin compared with placebo (between group difference of approximately 135 micromol/litre in favour of sapropterin).

There is no published minimal clinically important difference (MCID) for phenylalanine concentration, although in Levy et al. (2008) more people in the sapropterin group had phenylalanine concentrations within limits recommended in the European guidelines on the management of PKU (54%) compared with placebo (23%).

Trefz et al. 2009 and Muntau et al. 2017 reported that sapropterin for 10 or 26 weeks increased phenylalanine tolerance by 20 to 30 mg/kg/day compared with diet alone, although it's not clear from these studies whether patients would have been able to eat a normal, unrestrictive diet. There is no published MCID for phenylalanine tolerance, although a number of the low-quality, observational studies reported on the number of participants who could adopt an unrestricted diet while taking sapropterin. In Aldámiz-Echevarría et al. 2013, after 2 years treatment 78% of participants (28/36) taking sapropterin had an increase in phenylalanine tolerance, of whom 11 people could eat an unrestricted diet. In Aldámiz-Echevarría et al. 2015, after 12 months treatment with sapropterin 91% of participants (20/22) had an increase in phenylalanine tolerance, of whom 2 people could eat an unrestricted diet. In Feldmann et al. 2017, the authors reported that treatment with sapropterin allowed participants to eat a partially or entirely normal diet, although patient numbers are not reported.

No significant differences in physical growth parameters, including height, weight and head circumference, were observed from baseline to up to 2 years for children treated with sapropterin (Muntau et al. 2017, Longo et al. 2015, Aldámiz-Echevarría et al. 2013 and Aldámiz-Echevarría et al. 2015). There was also no significant difference in neuro-motor development from baseline to 26 weeks in children treated with sapropterin (Muntau et al. 2017). Most children in these studies had stable physical growth and neuro-motor development.

Sapropterin did not improve overall ADHD symptoms in adults and children with PKU, although some improvements in symptoms of inattention (being easily distracted or finding it hard to concentrate) were reported (Burton et al. 2015). Executive functioning (the set of processes that control behaviour) was reported in a 13-week study by Burton et al. 2015. Sapropterin did not improve executive functioning in adults with PKU, although children treated with sapropterin showed significant improvements in some elements of executive functioning. No significant improvements in clinician assessed global functioning were reported for adults or children with PKU (Burton et al. 2015). One study reported neuro-

cognitive functioning / intelligence, finding no significant decline in IQ from baseline to 2 years in children with PKU treated with sapropterin (Longo et al. 2015).

Health-related quality of life was poorly reported, with 2 observational studies reporting conflicting results (Feldmann et al. 2017, Cazzorla et al. 2014).

No evidence was found to determine whether or not sapropterin is a cost-effective treatment option for adults or children with PKU.

No evidence was found to determine which sub-groups of patients are more likely to benefit from treatment with sapropterin.

Studies included in this review report on long-term safety data on sapropterin for up to 3 years. The SPC for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in ≥1/10 people treated with sapropterin. Common adverse reactions (occurring in ≥1/100 to <1/10 people treated with sapropterin) include hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

The disease-orientated outcomes reported in this evidence review (blood phenylalanine concentration and phenylalanine tolerance) are from high quality RCTs. Many of the patient-orientated outcomes (quality of life and neuro-cognitive function) are only reported in lower quality studies, including uncontrolled observational studies, which have many limitations affecting their application to clinical practice.

Contents

1. Introduction

Background and current guidance

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterised by an increase of phenylalanine in the blood and body fluids (hyperphenylalaninaemia, HPA, Somaraju and Merrin 2015).

Phenylalanine is an essential amino acid provided by protein in the diet. A small amount of phenylalanine is used for protein synthesis, with the rest hydroxylised (converted) to another amino acid called tyrosine. People with PKU have a mutation in the gene that encodes an enzyme called phenylalanine hydroxylase, the enzyme responsible for the conversion of phenylalanine to tyrosine. The reduced levels of phenylalanine hydroxylase result in an accumulation of phenylalanine in the blood. Raised phenylalanine levels can be very harmful, damaging the brain. Infants with untreated PKU will appear to develop normally for the first few months of life, but will soon show signs of progressive encephalopathy (brain damage). Other features of PKU include growth failure, microcephaly, seizures, intellectual impairment and behavioural problems (Somaraju and Merrin 2015).

PKU is a rare condition, with an incidence of approximately 1 in 10,000 in people of European family origin. PKU is 1 of the 9 diseases tested for in the NHS newborn blood spot screening programme.

Severity of PKU is classified by the amount of phenylalanine present in the blood:

- classic (classical) PKU: phenylalanine levels above 1,200 micromol/litre
- mild PKU: phenylalanine levels between 600 and 1,200 micromol/litre
- mild hyperphenylalaninaemia: phenylalanine levels below 600 micromol/litre but above normal limits.

The European guidelines on the management of PKU were published in 2017. The guidelines recommend that children aged less than 12 years should maintain a blood phenylalanine level between 120 and 360 micromol/litre, and people aged 12 and over between 120 and 600 micromol/litre.

The aim of treatment in PKU is to lower phenylalanine levels to within safe limits, therefore preventing neurological damage. A phenylalanine-restricted diet is the standard treatment, designed to reduce phenylalanine levels while providing sufficient tyrosine and other nutrients needed for growth and development. This diet excludes all high protein foods (for example, meat, fish and dairy products) and tight control of food containing less natural protein (for example, some fruits and vegetables). Daily supplements containing amino acids are required. Such a diet is very restrictive in nature, the supplements have an unpleasant taste, and there is always a risk of nutritional deficiencies.

Phenylalanine-restricted diets may have a negative impact on a person's quality of life, and it has been reported that by early adulthood the many people with PKU do not comply with their diets (Somaraju and Merrin 2015). In a questionnaire study conducted in the United States, 88% of children with PKU aged 0 to 4 years had blood phenylalanine concentrations within clinic recommended limits (which was in line with European guideline recommendations for the majority of clinics). In comparison, only 33% of adults aged over 30 years had phenylalanine levels within recommended limits (Jurecki et al. 2017). Similar

results were reported by Brown and Lichter-Konecki (2015), who surveyed people with PKU, finding people aged 18 years or under were around 3 times more likely to keep their blood phenylalanine concentrations within recommended limits compared with older people. The study found around half of people with PKU had difficulty in managing their condition, including adherence to dietary restrictions. A systematic review by Enns et al. (2010) assessed outcome data for patients whose PKU was managed using a phenylalanine-restricted diet alone, finding sub-optimal outcomes for neurocognitive and psychosocial functioning, quality of life, brain pathology and physical growth.

A NICE Technology Appraisal has been proposed for Sapropterin for treating phenylketonuria (ID1475)

Product overview

Mode of action

Tetrahydrobiopterin (BH4) is a co-factor for phenylalanine hydroxylase. Tetrahydrobiopterin is thought to enhance the activity of residual phenylalanine hydroxylase. Sapropterin is a synthetic version of the naturally occurring tetrahydrobiopterin.

Only people with PKU who have residual phenylalanine hydroxylase activity will respond to treatment with sapropterin. The sapropterin summary of product characteristics [SPC] advises that phenylalanine levels should be checked before administering sapropterin and after 1 week of use at the recommended starting dose (10 mg/kg/day). If an unsatisfactory reduction in blood phenylalanine levels is observed, then the dose can be increased weekly to a maximum of 20 mg/kg/day, with continued weekly monitoring of blood phenylalanine levels over a one month period. The SPC defines a satisfactory response as reduction in blood phenylalanine levels of 30% or more from baseline, or attainment of the therapeutic blood phenylalanine goals defined for an individual patient by the treating physician. If phenylalanine levels are not reduced by this amount treatment with sapropterin should not be continued.

Note: some studies included in this evidence review refer to the intervention as tetrahydrobiopterin and some as sapropterin. For simplicity, this evidence review will use the name sapropterin throughout, irrespective of the term used in the original publication.

Regulatory status

Sapropterin is licensed for the treatment of HPA in adults, young people and children of all ages with PKU who have been shown to be responsive to treatment with sapropterin.

Sapropterin is also licensed for the treatment of HPA in adults, young people and children of all ages with tetrahydrobiopterin (BH4) deficiency, although use for this indication is outside of the scope of this evidence review.

Sapropterin has an orphan designation. Orphan medicines are:

- used to treat life-threatening or chronically debilitating conditions that affect no more than 5 in 10,000 people in the European Union, or
- medicines which, for economic reasons, would be unlikely to be developed without incentives.

Dosing information

The starting dose of sapropterin in adults and children with PKU is 10 mg/kg once daily. The dose is adjusted, usually between 5 and 20 mg/kg/day, to achieve and maintain adequate blood phenylalanine levels (SPC for sapropterin).

2. Methodology

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. Is sapropterin therapy clinically effective in patients with PKU whose:
   - PKU levels are controlled with dietary control alone
   - PKU levels are not controlled despite maximal dietary control

   in comparison to dietary control alone?

2. Is sapropterin therapy safe in patients with PKU whose:
   - PKU levels are controlled with dietary control
   - PKU levels are not controlled despite maximal dietary control

   in comparison to dietary control alone?

3. Is sapropterin therapy cost-effective in patients with PKU whose:
   - PKU levels are controlled with dietary control
   - PKU levels are not controlled despite maximal dietary control

   in comparison to dietary control alone?

4. Does the evidence review identify any subgroups who demonstrate better outcomes with sapropterin therapy?

The searches for evidence to support the use of sapropterin for phenylketonuria were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

3. Summary of included studies

This evidence review focusses on 3 double-blind randomised controlled trials (RCTs, Levy et al. 2007, Trefz et al. 2009, Burton et al. 2015) and an open-label RCT (Muntau et al. 2017).

Longer-term data are provided by 2 open-label extension studies (Lee et al. 2008, Burton et al. 2011). Five observational studies that report additional patient-orientated outcomes are also included (Longo et al. 2015, Aldámiz-Echevarría et al. 2015, Aldámiz-Echevarría et al. 2013, Feldmann et al. 2017, Cazzorla et al. 2014).

A summary of the included studies is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Levy et al. 2007 Double-blind RCT in 16 centres in North America and 14 centres in Europe.	89 adults and children aged ≥8 years (mean age 20.4 years, 58% male) with PKU responsive to sapropterin treatment. Participants were not following a phenylalanine restricted diet at baseline, and were required to continue their diet unchanged throughout the study period.	Sapropterin 10 mg/kg/day (n=42) Placebo (n=47)	Change in blood phenylalanine concentration[1] from baseline to week 6 Adverse events also reported (not primary outcome)
Lee et al. 2008 Open-label extension study to Levy et al. (2007) Conducted in 26 centres in North America and Europe, including centres in the UK.	80 adults and children aged ≥8 years (mean age 20.4 years, 59% male) who had previously taken part in the RCT by Levy et al. 2007, provided they had received ≥80% of the scheduled doses. Participants were not following a phenylalanine restricted diet at baseline, and were required to continue their diet unchanged throughout the study period.	Sapropterin 5, 10 or 20 mg/kg/day (n=80) No control	Change in blood phenylalanine concentration[1] up to week 22 Adverse events also reported (not primary outcome)
Trefz et al. 2009 Double-blind RCT in 15 centres across Europe and the United States.	45 children (mean age 7.5 years, 58% male) with PKU responsive to sapropterin treatment. All participants were on a phenylalanine-restricted diet which was maintained throughout the study period. Starting at week 3 phenylalanine supplements were introduced.	Sapropterin 20 mg/kg/day (n=33) Placebo (n=12)	Mean daily phenylalanine supplement tolerated[1] over 10 weeks Adverse events also reported (not primary outcome)
Burton et al. 2011 Open-label extension study to Lee et al. 2008 and Trefz et al.	111 people (mean age 16.4 years, 60.4% male) with PKU responsive to sapropterin. The study had no dietary restrictions and phenylalanine	Sapropterin 5 mg to 20 mg/kg/day (n=111) No control	Long-term safety – adverse events up to 3 years

2009 Conducted in 15 centres in the United States, Canada and Europe (including sites in the UK)	intake was not monitored.		
Muntau et al. 2017 Open-label, randomised control trial in 22 centres in 9 countries, including 2 centres in the UK.	56 children aged less than 4 years (mean age 21 months, 59% male) with PKU responsive to sapropterin. All participants followed a phenylalanine-restricted diet and were required to have good phenylalanine control (between 120 and 360 micromol/litre for 4 months before screening). Participants could adjust their dietary intake of phenylalanine, with intake guided by blood phenylalanine concentration.	Sapropterin 10 mg/kg/day (could be increased to 20 mg/kg/day after 4 weeks if phenylalanine tolerance not increased by >20% compared with baseline) (n=27) Phenylalanine-restricted diet only (n=29)	Change in phenylalanine tolerance[1] from baseline to week 26 Adverse events also reported (not primary outcome)
Burton et al. 2015 Double-blind, randomised control trial in 36 centres across the United States and Canada.	118 adults and children aged 8 year and over (mean age approximately 20 years, 58% male) with PKU responsive to sapropterin. Participants were required to continue on their current diet. The authors do not provide details on the diets the participants followed, although raised blood phenylalanine levels at baseline suggest that at least some people in the study were not following a strict phenylalanine-restricted diet.	Sapropterin (dose not reported) (n=61) Placebo (n=57)	Change in ADHD symptoms at 13 weeks and Change in global function at week 13 Adverse events also reported (not primary outcome)
Longo et al. 2015 Open-label, prospective, uncontrolled study (2 year results from a 7 year study) Multicentre study	65 children aged 0 to 6 years (mean age 3.14 years) at screening with PKU / HPA and at least 2 blood phenylalanine concentrations ≥360 micromol/ litre taken at least 3 days apart. All participants had a phenylalanine-restricted diet during the study, designed to keep phenylalanine within recommended limits.	Sapropterin 20 mg/kg/day. Dose reductions were permitted after week 5 for children who did not tolerate this dose (n=65) No control	Change in neurocognitive function from baseline to 2 years (interim analysis from 7 year study). The tool used to measure function determined by the child's age. Adverse events also reported (not primary outcome)
Aldámiz-Echevarría et al. 2013 Retrospective	38 children and young people aged ≤16 years with PKU responsive to sapropterin. All participants were required to	Sapropterin[2] (dose not reported) (n=38) Diet alone (n=76)	Physical growth parameters from baseline up to 2 years

longitudinal study in 13 centres in Spain	be on a phenylalanine-restricted diet. Over the course of the study, people treated with sapropterin gradually increased their intake of natural protein and reduced intake of amino acid supplements.		
Aldámiz-Echevarría et al. 2015 Retrospective longitudinal study in 14 centres in Spain	22 children (0 to 4 years) with PKU responsive to sapropterin. All participants were required to have good adherence to their prescribed diet, although the authors do not provide details on the diets of people taking sapropterin, and the degree of phenylalanine restriction. Over the course of the study, people treated with sapropterin gradually increased their intake of natural protein and reduced intake of amino acid supplements.	Sapropterin[2] (dose not reported) (n=22) Diet alone (n=44)	Physical growth parameters from baseline up to 1 year
Feldmann et al. 2017 Prospective cohort study in single centre in Germany	112 adults and children (aged ≥4 years) with PKU. 41.1% (46/112, 24 children) of participants responded to sapropterin and continued treatment. Participants who did not respond to sapropterin (66/112, 58.9%) remained in the study on diet alone, acting as controls. For people taking sapropterin, dietary phenylalanine was increased over 6 weeks through the addition of natural protein.	Sapropterin 20 mg/kg/day (n=46) Diet alone (n=66)	Health-related quality of life from baseline to 6 months, measured using KINDL[R] (for patients) or ULQIE (for parents)
Cazzorla et al. 2014 Prospective observational study in 2 centres in Italy	43 people with PKU. 22 participants had mild PKU (blood phenylalanine 600 to 1,200 micromol/ litre) responsive to sapropterin, and were treated with sapropterin. Mean age 15.4 years. 21 participants had classical PKU (blood Phe >1,200 micromol/ litre) and were treated with diet alone. Mean age 18.9 years. The authors did not report on the diets of the participants taking sapropterin. The authors	Sapropterin[2] 10 mg/kg/day (mild PKU) (n=22) Diet alone (classical PKU) (n=21)	Quality of life, measured using: The Pediatric Quality of Life Inventory (PedsQL) in children (6 to 16 years) The World Health Organisation QoL score (WHOQOL-100) in adults (≥18 years) Treatment duration varied between patients (range 1 to 11 years.

	state that people treated with sapropterin were allowed 'relevant relaxation of the dietary-restriction', although more details are not provided.		

[1] There is no published minimal clinically important difference for this outcome, see the Results section for a discussion on the clinical relevance of these results.

[2] The authors report that the intervention was given as 6R-tetrahydrobiopterin (6R-BH_4) until 2009, and sapropterin thereafter.

Abbreviations: ADHD, Attention deficit and hyperactivity disorder; HPA, hyperphenylalaninaemia; KINDL^R, Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern und Jugendlichen;

In English: Questionnaire to assess the health-related quality of life of children and adolescents; PKU, phenylketonuria; RCT, randomised controlled trial; ULQIE, Ulm Quality of Life Inventory for Parents

Details of the excluded studies are listed in the section on evidence selection.

4. Results

An overview of the results for clinical effectiveness and safety and tolerability can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

Clinical effectiveness

This section considers whether sapropterin is clinically effective in patients with PKU whose i) PKU levels are controlled with dietary control alone, and ii) PKU levels are not controlled despite maximal dietary control, both compared to dietary control alone.

Blood phenylalanine concentration

In a double-blind RCT by Levy et al. (2007) involving 89 adults and children (mean age 20.4 years) with PKU responsive to sapropterin treatment, people treated with sapropterin for 6 weeks had significantly lower blood phenylalanine compared with people treated with placebo (mean difference between groups −245 micromol/litre, standard deviation [SD] 52.5, p=0.0002). The same study found a higher proportion of people were able to maintain their blood phenylalanine below 600 micromol/litre at 6 weeks when treated with sapropterin (22/41, 54%) compared with placebo (11/47, 23%).

Lee et al. (2008) reported on a single-arm, open-label extension to Levy et al. (2007), in which 80 participants were treated with sapropterin for 22 weeks. Sapropterin reduced blood phenylalanine concentrations by a mean of 190.5 micromol/litre at 22 weeks (from 844.0 micromol/litre at baseline).

The double-blind RCT by Trefz et al. (2009) found that in 45 children (mean age 7.5 years) with PKU responsive to sapropterin, children treated with sapropterin for 3 weeks had significantly lower phenylalanine concentrations compared with placebo (mean between group difference −135.2 (95% −187.9 to −82.5, p<0.001). All children in this study adhered to a phenylalanine-restricted diet and had low phenylalanine levels at baseline (275 micromol/litre in the sapropterin group).

This reviewer could not identify a published minimal clinically important difference (MCID) for phenylalanine concentration. The SPC for sapropterin defines a satisfactory response to treatment as a reduction of 30% or more in phenylalanine concentration from baseline or attainment of target blood levels. All participants in Levy et al. were required to have reduction in blood phenylalanine of 30% or more after 8 days treatment with sapropterin, and were considered sapropterin responders. After 6 weeks treatment with sapropterin, people in the Levy et al. study had a mean reduction in phenylalanine level of 28%, of whom over half had phenylalanine levels within the recommended limits set out in the European guidelines on the management of PKU. Similar results were reported in the extension study by Lee et al. with a mean reduction of 23% reported after 22 weeks treatment with sapropterin.

Phenylalanine tolerance, dietary restrictions and nutrition

In a 2009 double-blind RCT by Trefz et al. (n=45), at week 10, children treated with sapropterin tolerated significantly higher doses of phenylalanine supplements compared with the placebo group (mean treatment difference 17.7 mg/kg/day, p<0.001). Mean total phenylalanine daily intake (dietary plus supplements) was 43.8 mg/kg/day in the sapropterin group and 23.5 mg/kg/day in the placebo group.

Muntau et al. (2017), an open-label RCT, found that children with PKU (n=56) could tolerate significantly more phenylalanine supplements after 26 weeks treatment with sapropterin compared with children treated by diet alone (80.6 mg/kg/day and 50.1 mg/kg/day respectively, adjusted between group difference of 30.5 mg/kg/day, 95% CI 18.7 to 42.3, p<0.001). In the same study children in the sapropterin group could also tolerate significantly more dietary phenylalanine compared with children managed by diet alone (75.7 mg/kg/day and 42.0 mg/kg/day respectively, adjusted between group difference 33.7 mg/kg/day, 95% CI 21.4 to 45.9, p<0.001). Although participants in the Muntau et al. (2017) could increase their dietary phenylalanine intake, the authors do not report how this affected an individual's diet (for example, what sources of natural protein they could eat) or whether any participants could eat a normal, non-restrictive diet.

Participants in the study by Levy et al. (2007) were not following a phenylalanine-restricted diet and were required to have a raised blood phenylalanine concentration at baseline (600 micromols/litre or more, later reduced to 450 micromol/litre). As reported above, phenylalanine concentrations dropped from 843 micromol/litre to 607 micromol/litre after 6 weeks treatment with sapropterin, despite participants eating a non-restricted diet. Most participants (85%) in the sapropterin group were aged over 12 years. Similar results were seen in the 22 week open-label extension by Lee et al. (2008), with mean phenylalanine levels at 652 micromol/litre after 22 weeks treatment with sapropterin. It should be noted that the mean phenylalanine level was still above the upper safe limit of 600 micromol/litre recommended for people aged over 12 years in the European guidelines on the management of PKU. However, in the study by Levy et al., after 6 weeks treatment with sapropterin 54% of participants had phenylalanine levels below 600 micromol/litre, compared with 23% in the placebo group. This suggests that a proportion of people with PKU may be able to maintain safe phenylalanine levels when taking sapropterin while not adhering to a restrictive diet.

In the 2 studies by Aldámiz-Echevarría et al. (2013 and 2015), children treated with sapropterin gradually increased their intake of high-protein foods (for example, milk and dairy products) and moderate-protein foods (for example, cereals), and reduced intake of

amino acid supplements. Patients (or their parents) weighed and recorded the amount of food and drink consumed during the 3 days before their check-ups.

In Aldámiz-Echevarría et al. 2013, at the 2-year follow-up 28/36 participants (78%) in the sapropterin had an increase in phenylalanine tolerance, of whom 11 participants managed to gradually adopt an unrestricted diet. For the 17 participants who had increased phenylalanine tolerance but still required a restricted diet, phenylalanine tolerance increased by approximately 330 mg/day at the 2-year follow-up. For the 5-year follow-up, data were available for 10 patients treated with sapropterin, of whom 6 patients had an increase in phenylalanine tolerance and 2 patients had steady phenylalanine tolerance (results for 2 patients not reported). Within the group with increased phenylalanine tolerance, 2 patients could adopt an unrestricted diet, with the remaining 4 patients still requiring a restricted diet. The authors report that natural protein intake increased at the end of the 5-year follow-up in the sapropterin group, and was 3 times higher compared with the diet only group.

In Aldámiz-Echevarría et al. 2015, 22 children were treated with sapropterin for 1 year, of whom 20 children had an increase in phenylalanine tolerance and in 2 children phenylalanine tolerance remained stable. Of the 20 children with increased phenylalanine tolerance, 2 children were able to eat an unrestricted diet, while the other 18 children still needed to remain on a restricted diet. In the 18 children who still required a phenylalanine-restricted diet, the daily intake of natural protein increased by 10 grams from baseline.

In Feldmann et al. 2017, in 46 adults and children treated with sapropterin, mean dietary intake of phenylalanine increased from 13.8 mg/kg/day at baseline to 35.5 mg/kg/day at 6 weeks. During the same time period the amount of amino acid supplements reduced from 0.76 gram/kg/day to 0.46 gram/kg/day. The authors reported that sapropterin led to a relaxation in phenylalanine-restricted diets, with patients having a partially or entirely normal diet, although details, including patient numbers, are not reported.

Patients who received sapropterin in the study by Cazzorla et al. 2014 were allowed a “relevant relaxation of the dietary-restriction”, although the authors do not discuss how many people in the study could eat a normal, non-restricted diet.

Physical growth

An open-label RCT by Muntau et al. (2017) reported on physical growth parameters in 56 children with PKU aged less than 4 years who were treated with sapropterin or diet only for 26 weeks. There was no statistically significant difference between groups for any growth parameter. The authors note that children in both groups had stable growth parameters.

In an open-label, single-arm prospective study by Longo et al. (2015), there was no significant difference in growth rate between baseline and 2-year follow-up for any physical growth parameters (height, weight and head circumference) for children aged 0 to 6 years treated with sapropterin, with Z-scores of slightly below 0.5 maintained throughout the study period for all parameters. In total, 55 participants were included in the 2-year analysis. Z-scores report how many standard deviations from the mean a measurement sits. A Z-score of 0 is equal to the mean, or the 50th percentile for growth. A Z-score of −1 is equal to 1 standard deviation below the mean, and a Z-score of +1 is equal to 1 standard deviation above the mean.

In the retrospective longitudinal study by Aldámiz-Echevarría et al. 2013, there was no significant change from baseline to 2 years or 5 years in mean Z-score for any growth parameter in children and young people treated with sapropterin or diet alone. In a similar study from the same authors (Aldámiz-Echevarría et al. 2015) there was also no difference in any growth parameter between the sapropterin and diet-only groups, and from baseline to 6- or 12-months within either group.

Global function

The double-blind RCT by Burton et al. (2015, n=118) investigated global function in adults and children with PKU, measured using the Clinical Global Impression of Improvement (CGI–I) scale. There was no significant difference in the proportion of people who were much improved or very much improved (CGI-I scale 1 or 2) in the sapropterin group (21.7%) compared with placebo (26.3%, relative risk ratio 0.87, 95% CI 0.46 to 1.64, p=0.670).

Executive function

Burton et al. (2015, n=118) reported on executive function (the set of cognitive processes that control behaviour), measured using the Global Executive Composite (GEC), Metacognition Index (MI) and Behaviour Regulation Index (BRI) from the Behaviour Rating Inventory of Executive Function (BRIEF) tool. Results are reported as standard T-scores. Standard T-scores have a mean of 50, with higher scores indicating poorer executive function. The authors state that T-scores above 65 are typically considered clinically significant, although T-scores above 60 on the BRIEF self-reports may also warrant clinical interpretation.

Results are reported separately for children and young people, and adults. Baseline scores for EC, MI and BRI were approximately 60 points, suggesting participants may have impaired executive functioning.

After 13 weeks treatment, no significant difference in any score was reported for sapropterin compared with placebo for adults.

After 13 weeks treatment, children and young people treated with sapropterin had significant improvements in GEC and MI score compared with placebo (mean between group difference −4.1 and −4.4 respectively, both $p<0.05$). The BRI score was numerically lower in the sapropterin group compared with placebo (mean between group difference −3.4, p=0.053), although the difference was not statistically significant.

Neuro-cognitive function

Neuro-cognitive function was reported by the open-label, single-arm prospective study by Longo et al. (2015). The tool used to the assess function varied by age group. At baseline the average Full Scale Intelligence Quotient (FSIQ) score across the study population was not significantly different from the population norm of 100. The authors reported that there was no significant decline in FSIQ over the 2 year follow-up, and that after starting sapropterin no infant or toddler had an FSIQ score of less than 85. However, without a control group it is not clear whether these results reflect the natural development in PKU or neuro-protection from sapropterin.

Neuro-motor development

Muntau et al. (2017) found no significant difference in neuro-motor development at 12 and 26 weeks in children treated with sapropterin compared with diet alone. Most participants in both treatment groups had normal neuro-motor development.

Attention deficit and hyperactivity disorder (ADHD) symptoms

A double-blind RCT by Burton et al. (2015) reported on attention deficit and hyperactivity disorder (ADHD) symptoms in 38 adults and children with PKU, measured using the ADHD Rating Scale/Adult Self-Report Scale (ADHD RS/ASRS). There was no statistically significant difference between sapropterin and placebo in change from baseline to week 13 for ADHD RS/ASRS total score (between group difference −4.2, 95% CI −8.9 to 0.6, p=0.085) or ADHD RS/ASRS hyperactivity/impulsivity subscale score (between group difference −1.0, 95% CI −3.4 to 1.4, p=0.396). A statistically significant difference between groups in favour of sapropterin was observed at 13 weeks for the ADHD RS/ASRS inattention subscale score (−3.4, 95% CI −6.6 to −0.2, p=0.036).

Health-related quality of life

Data on health-related quality of life is limited to 2 observational studies by Feldmann et al. 2017 (n=112) and Cazzorla et al. 2014 (n=43). The studies reported conflicting results.

Feldman and colleagues found no improvement in quality of life (measured using the KINDL^{R} questionnaire) in children treated with sapropterin or their parents, compared with children who had not responded to sapropterin and were managed by diet-alone.

Cazzorla et al. reported significant improvements in quality of life (measured using the PedsQL or WHOQOL-100 questionnaires) in people with mild PKU treated with sapropterin compared with people with classical PKU treated with diet alone. Both studies were of low quality and had a high risk of bias, meaning it is not possible to draw firm conclusions on the impact of sapropterin on quality of life.

Safety and tolerability

This section considers whether sapropterin compared with dietary control alone is safe in patients with PKU whose i) PKU levels are controlled with dietary control alone, and ii) PKU levels are not controlled despite maximal dietary control.

The short-term safety of sapropterin is reported in the RCTs by Levy et al. (2007) and Trefz et al. (2009), with longer-term safety data provided by 2 open-label extension studies (Lee et al. 2008 and Burton et al. 2011) and RCTs by Burton et al. (2015) and Muntau et al. (2017).

Between 63% and 100% of participants in individual trials reported at least one adverse event. The majority of adverse events were mild or moderate in severity, and adverse events leading to withdrawal from study were rare.

The most frequently reported adverse events in the clinical trials included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia.

In the European Public Assessment report (EPAR) for sapropterin the regulators concluded that sapropterin was well tolerated. The EPAR states that hypophenylalaninaemia (defined as blood phenylalanine 26 micromol/litre or less) was more common in people treated with

sapropterin compared with placebo, noting that this is an expected result of sapropterin lowering phenylalanine levels and may indicate a need to increase dietary phenylalanine or adjust the sapropterin dose.

The SPC for sapropterin reports headache and rhinorrhoea as very common adverse reactions, occurring in ≥1/10 people treated with sapropterin. Common adverse reactions (occurring in ≥1/100 to <1/10 people treated with sapropterin) listed in the SPC are hypophenylalaninaemia, pharyngolaryngeal pain, nasal congestion, cough, diarrhoea, vomiting, abdominal pain, dyspepsia and nausea.

Cost effectiveness

This section considers whether sapropterin is cost-effective in 2 groups of people with PKU:

i) those whose PKU levels are controlled with dietary control, and
ii) those whose PKU levels are not controlled despite maximal dietary control.

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of sapropterin with diet alone in people with PKU. None of the studies included in this evidence review included an outcome investigating cost-effectiveness.

Benefits of treatment by subgroup

This section considers whether there is evidence for subgroups of people who demonstrate better outcomes with sapropterin therapy.

The most clearly defined subgroup of people who are more likely to benefit from sapropterin are those who are responsive to sapropterin. In the studies included in this evidence review, treatment with sapropterin was limited to people who had a positive response to a short, test course of sapropterin. The methods for determining response varied between studies, but in general, participants received a 2 to 4 week course of sapropterin and had their phenylalanine re-measured. Participants with a marked reduction in phenylalanine from baseline, normally 20-30%, were considered sapropterin responders and continued treatment with sapropterin.

Most studies included in this evidence review did not report efficacy and safety by subgroup, such as age and baseline phenylalanine concentration.

In Burton et al. (2015), children and young people treated with sapropterin were more likely to have improvements in executive function compared with adults.

Longo et al. (2015) reported phenylalanine tolerance and phenylalanine concentration by age band (<1 year, 1–2, 3–4 and 5–6 years), although the number of children in each group was small (n=10 to n=19). Children in each age group had an increase in phenylalanine tolerance over the 2 year study period. Overall phenylalanine concentration fell over the study period, although in children aged 3–4 years the level returned to baseline after 2 years.

It is not possible to identify subgroups of people who are more likely to benefit from treatment with sapropterin based in the studies included in this evidence review.

5. Discussion

Evidence strengths and limitations

The studies included in this evidence review are of variable quality, ranging from high quality, double-blind RCTs, to low quality, retrospective observational studies. The lower quality studies were included in the review because they reported on patient-orientated outcomes which were not included in the higher quality studies.

The included RCTs were all small, randomising fewer than 100 participants across all treatment arms, which is usual for rare conditions such PKU due to the limited number of eligible participants. It is reassuring that many of the RCTs reported power calculations, and most would appear to have been adequately powered for their primary outcome. The older, phase III RCTs included in this review were of short duration (6 to 10 weeks), although open-label extension studies and more recently published RCTs provide longer term efficacy and safety data.

It is difficult to assess the clinical relevance of many of the outcomes discussed in this evidence review because they do not have published minimal clinically important differences (MCIDs).

The disease-orientated outcomes reported in this evidence review, namely blood phenylalanine concentration and phenylalanine tolerance, are from high quality RCTs. Many of the patient-orientated outcomes, for example quality of life and neuro-cognitive function, are only reported in lower quality studies, including uncontrolled observational studies, which have many limitations affecting their application to clinical practice.

No evidence was found to determine whether or not sapropterin is a cost-effective treatment option for adults or children with PKU.

Other treatments

No other treatments are generally considered at the same stage in the treatment pathway for phenylketonuria as sapropterin.

6. Conclusion

The studies included in this evidence review suggest that sapropterin reduces blood phenylalanine concentrations and increases phenylalanine tolerance in adults and children with PKU compared with phenylalanine restricted diet alone. These effects appear to be maintained with long-term treatment. People treated with sapropterin in the studies were able to increase the natural protein in their diet, and although this is difficult to quantify as it was poorly reported in the included studies, a small proportion of people were able to eat a normal, non-restrictive diet.

The impact of sapropterin on development and day-to-day living is less clear. Sapropterin does not appear to produce a meaningful improvement in physical growth, neuro-motor development or global functioning compared with diet alone, although these outcomes were reported in fewer studies. Sapropterin did not improve overall ADHD symptoms in people with PKU, although improvements were reported for inattention symptoms. No improvements in executive functioning were observed in adults treated with sapropterin,

although improvements in elements of executive functioning were reported in children. Quality of life and neuro-cognitive function / intelligence were poorly reported, and the poor quality of the studies reporting these outcomes prevent firm conclusions being made.

All the studies assessed response to sapropterin treatment before starting the medicine, although the methods used to do this varied. In line with the marketing authorisation only people with a positive response were continued on sapropterin.

Adverse events were relatively common in people treated with sapropterin, although these were generally mild to moderate in severity, and did not require treatment to be stopped. Adverse events reported in studies included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia.

7. Evidence summary table

Use of sapropterin to treat phenylketonuria							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: Levy et al. 2007							
P1- Double-blind, randomised control trial	16 centres in North America and 14 centres in Europe. 89 adults and children aged ≥8 years (mean age 20.4 years, 58% male) with phenylketonuria responsive to sapropterin treatment (defined as a reduction of 30% or more in blood phenylalanine concentration after sapropterin 10 mg/kg for 8 days). Participants were required to have blood phenylalanine ≥600 micromols/ litre (450 micromols/ litre after protocol amendment).	Sapropterin 10 mg/kg daily (n=42) Placebo (n=47) Participants were not following a phenylalanine restricted diet at baseline, and were required to continue their diet unchanged throughout the study period.	Primary Clinical effectiveness	Change in blood phenylalanine concentration[1] from baseline to week 6.	The mean change in the sapropterin group was −235.9 micromol/litre (from 842.7 micromol/litre at baseline). The mean change in the placebo group was +2.9 micromol/litre (from 888.3 micromol/litre at baseline). Statistically significant difference between groups of −245 micromol/litre (SD 52.5), p=0.0002.	7/10	Direct study focusing on people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	Proportion of patients with blood phenylalanine concentration below 600 micromol/ litre at week 6.	In the sapropterin group, 17% (7/41) had blood phenylalanine levels <600 micromol/litre at screening. This increased to 54% (22/41) by week 6. In the control group, 19% (9/47) had blood phenylalanine levels <600 micromol/litre at screening. This increased to 23% (11/47) by week 6.		

			Secondary Safety	Adverse events	Across the whole study population, 55/88 participants (63%) reported a total of 148 adverse events. Adverse events possibly related to drug-treatment were reported by 23% (11/47) of people in the sapropterin group and 20% (8/41) of people in the placebo group. There was no statistically significant difference between groups (p=0.8). No participants withdrew from the study due to adverse events. The most common adverse events in the sapropterin group were upper respiratory tract infection (17%), headache (10%), vomiting (5%), diarrhoea (5%) and pyrexia (5%).		
Critical appraisal summary: This is multicentre, double-blind, randomised controlled trial with a low risk of bias. Randomisation methods are reported by the authors and it would appear that allocation was concealed. All participants are accounted for, and intention-to-treat analysis was carried out. A power calculation is reported and the study would appear to be adequately powered. Baseline characteristics were generally comparable across treatment arms. The study is limited by a short, 6 week duration and a focus on disease-orientated efficacy outcomes. [1] There is no published minimal clinically important difference for this outcome, see the Results section for a discussion on the clinical relevance of these results.							
Study reference 2: Lee et al. 2008							
P1- Open-label extension study to Levy et al. 2007	26 centres in North America and Europe, including centres in the UK. 80 adults and children aged ≥8 years (mean age 20.4 years, 59% male) who had previously taken part in the RCT by Levy et al. 2007, provided they had received ≥80% of the scheduled doses in a previous phase II study.	All participants received sapropterin (n=80). There were 3 treatment phases: Forced dose-titration period (6 weeks): sapropterin 5, 10 and 20 mg/kg/day consecutively for 2 weeks each.	Primary Clinical effectiveness	Change in plasma phenylalanine concentration[1] up to week 22.	Across all doses of sapropterin the mean plasma phenylalanine concentration reduced from 844.0 micromol/litre at baseline to 645.2 micromol/litre at week 10. This reduction was maintained until week 22 (652.2 micromol/litre). Mean change in phenylalanine from baseline to week 22 was −190.5 micromol/litre.	7/10	Direct study focusing on people with the indication and characteristics of interest.

		Dose analysis period (4 weeks): sapropterin 10 mg/kg/day. Fixed dose period (12 weeks): sapropterin 5, 10 or 20 mg/kg/day, dose determined by phenylalanine levels at weeks 2 and 6 of the dose titration phase. Participants were not following a phenylalanine restricted diet at baseline, and were required to continue their diet unchanged throughout the study period.					
			Secondary Safety	Adverse events	In total, 260 adverse events were reported by 68/80 participants (85%). No participants withdrew from the study due to adverse events. 82/260 adverse events (32%) in 31/80 participants (39%) were considered possibly or probably related to sapropterin treatment. Adverse events probably related to sapropterin were upper abdominal pain, nausea, headache, dizziness and increased alanine amino-transferase.		
Critical appraisal summary: This is an open-label, extension study to a double-blind RCT. The open-label design means the study is susceptible to bias. The study required participants to have had good adherence to sapropterin in a previous trial, this may have introduced bias. All participants are accounted for. The lack of a control arm prevents conclusions on the relative efficacy and safety of sapropterin. [1] There is no published minimal clinically important difference for this outcome, see the Results section for a discussion on the clinical relevance of these results.							
Study reference 3: Trefz et al. 2009							

P1- Double-blind, randomised control trial	15 centres across Europe and the United States. 45 children (mean age 7.5, 58% male) with phenylketonuria responsive to sapropterin treatment (defined as a reduction of 30% or more in blood phenylalanine concentration after sapropterin 20 mg/kg for 8 days and a blood phenylalanine concentration of 300 micromol/ litre or less on day 8). Inclusion criteria: aged 4 to 12 years, estimated phenylalanine tolerance ≤1,000 mg/day, currently controlled with phenylalanine-restricted diet (mean blood phenylalanine concentration ≤480 micromol/ litre over the 6 months before the study and at screening).	Sapropterin 20 mg/kg/day (n=33) Placebo (n=12) All participants were on a phenylalanine-restricted diet which was maintained throughout the study period. Beginning at week 3, phenylalanine supplements were introduced, the dose of which was adjusted every 2 weeks (up to a maximum of 50mg/kg/day) to achieve the maximum phenylalanine dose possible while maintaining good control (defined as blood phenylalanine concentration <360 micromol/ litre.	Primary Clinical effectiveness	Mean phenylalanine supplement tolerated[1] at week 10 compared with baseline. Participants had to maintain good blood phenylalanine control, defined as <360 micromol/ litre.	At week 10, people in the sapropterin group tolerated a mean phenylalanine supplement of 20.9 mg/kg/day (95% confidence interval [CI] 15.4 to 26.4, p<0.0001 compared with baseline, participants received 0 mg/kg/day at baseline). People in the placebo group tolerated a mean phenylalanine supplement of 2.9 mg/kg/day at week 10. The adjusted mean difference between treatment groups was 17.7 mg/kg/day (95% CI 9 to 27, p<0.001, secondary outcome).	8/10	Direct study focusing on people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	Mean total phenylalanine (supplements plus diet) tolerated[1] at week 10 compared with baseline. Participants had to maintain good blood phenylalanine control, defined as <360 micromol/ litre.	At week 10, the total phenylalanine intake in the sapropterin group reached 43.8 mg/kg/day (SD 24.6), from 16.3 mg/kg/day at baseline (p<0.0001). People treated with placebo had a mean total phenylalanine intake of 23.5 mg/kg/day (SD 12.6) compared with 16.8 mg/kg/day at baseline (no statistically significant difference).		

			Secondary Clinical effectiveness	Change in blood phenylalanine concentration[1] from baseline to week 3	The mean change in the sapropterin group was −148.5 micromol/litre (95% CI −196 to −101) from 275.7 micromol/litre at baseline. The mean change in the placebo group was −96.6 micromol/litre, baseline level not reported. At week 3, the mean difference in blood phenylalanine concentration between groups was −135.2 (95% CI −187.9 to −82.5, p<0.001).		
			Secondary Safety	Adverse events	A total of 128 adverse events were reported in 34/45 participants (76%). The most frequently reported adverse events by people taking sapropterin were rhinorrhoea (21%), headache (21%) and cough (15%). Adverse events considered to be possibly related to study treatment were reported by a similar proportion of people in the sapropterin group (27%) and the placebo group (25%). Two serious adverse events occurred: 1 streptococcal infection in the sapropterin group and 1 case of appendicitis in the placebo group. Neither were considered to be related to study treatment. No participants withdrew from the study due to adverse events.		
Critical appraisal summary: This is a multicentre, double-blind, randomised controlled trial with a low risk of bias. Randomisation and blinding methods are reported by the authors and it would appear that allocation was concealed. All participants are accounted for, and intention-to-treat analysis was carried out. A power calculation is reported and the study would appear to be adequately powered. Baseline characteristics were comparable across treatment arms.							

The study is limited by a short, 10 week duration and a focus on disease-orientated efficacy outcomes. [1] There is no published minimal clinically important difference for this outcome, see the Results section for a discussion on the clinical relevance of these results.							
Study reference 4: Burton et al. 2011							
P1- Open-label extension study to Lee et al. 2008 and Trefz et al. 2009	15 centres in the United States, Canada and Europe (including sites in the UK) 111 people with PKU responsive to sapropterin who had completed Lee et al. 2008 and Trefz et al. 2009, or withdrew from Trefz et al. 2009 due to elevated phenylalanine concentrations. Mean age was 16.4 years (range 4 to 50) and 60.4% were male.	Sapropterin 5 mg to 20 mg/kg/day adjusted to control blood phenylalanine concentrations according to local clinical site recommendations (n=111) No control The mean duration of treatment was 658.7 days (range 56 to 953 days). The study had no dietary restrictions and phenylalanine intake was not monitored. During the study by Lee et al, participants were not following a restricted diet, whereas in Trefz et al. participants followed a phenylalanine restricted diet.	Primary Safety	Adverse events up to 3 years	Adverse events were reported by 93/111 participants (83.8%), with 37/111 participants (33.3%) reporting drug-related adverse events. The most common drug-related adverse events were viral gastroenteritis, vomiting, and headache (each occurring in 4.5% of participants). 21/111 participants (18.9%) withdrew from the study early. 3 participants withdrew because of drug-related adverse events (difficulty concentrating, clinically significant decreased platelet count, and intermittent diarrhoea).	8/10	Direct study focusing on people with the indication and characteristics of interest.
Critical appraisal summary: This is an open-label, extension study to a double-blind RCT. The open-label design means the study is susceptible to bias. Participants were required to have completed the run-in RCTs. All participants are accounted for. The lack of a control arm prevents conclusions on the relative safety of sapropterin.							
Study reference 5: Muntau et al. 2017							

P1- Open-label, randomised control trial	22 centres in 9 countries, including 2 centres in the UK. 56 children aged less than 4 years (mean age 21 months, 54% male) with sapropterin responsive phenylketonuria. The mean age at diagnosis was 30 days. 46% of participants were diagnosed with mild hyperphenylalaninaemia (HPA, phenylalanine 120-600 micromol/ litre), 32% with mild phenylketonuria (Phe 600-1,200 micromol/ litre) and 21% with classical phenylketonuria (phenylalanine >1,200 micromol/ litre.	Sapropterin 10 mg/kg/day (could be increased to 20 mg/kg/day after 4 weeks if phenylalanine tolerance not increased by >20% compared with baseline) (n=27) Diet only (n=29) All participants followed a phenylalanine-restricted diet and were required to have good phenylalanine control (between 120 and 360 micromol/litre for 4 months before screening). Participants could adjust their dietary intake of phenylalanine, with intake guided by blood phenylalanine concentration.	Primary Clinical effectiveness	Change in phenylalanine tolerance[1] from baseline to week 26 Phenylalanine tolerance was defined as the daily amount of phenylalanine that could be ingested while keeping mean blood phenylalanine concentration with target range (120-360 micromol/ litre) by dietary phenylalanine adjustments.	Prescribed phenylalanine At week 26, people treated with sapropterin could tolerate significantly more phenylalanine supplement (80.6 mg/kg/day) compared with for people treated with diet alone (50.1 mg/kg/day), adjusted between group difference 30.5 mg/kg/day, 95% CI 18.7 to 42.3, p<0.001, statistically significant difference. Dietary phenylalanine At week 26, people treated with sapropterin could tolerate 75.7 mg/kg/day of dietary phenylalanine, compared with 42.0 mg/kg/day in the diet only group. Statistically significant difference between groups (adjusted difference between groups 33.7 mg/kg/day, 95% CI 21.4 to 45.9, p<0.001).	7/10	Direct study focusing on people with the indication and characteristics of interest
			Secondary Clinical effectiveness	Neuro-motor development	No statistically significant difference between groups in any neuro-motor developmental milestones at baseline, week 12 and week 26. The authors note that most participants in both treatment groups had normal neuro-motor development, including fine motor, gross motor, language, personal function and social function.		
			Secondary Clinical effectiveness	Physical growth parameters	No statistically significant between groups for any physical growth parameters. Participants in both treatment groups had stable growth parameters, including body mass index standard deviation		

					score (SDS), height SDS, maximum occipital-frontal head circumference SDS and weight SDS.		
			Secondary Safety	Adverse events	The safety population included 54 participants. All participants across both treatment groups (54/54, 100%) reported at least 1 adverse events, 560 adverse events across both groups. In the sapropterin group, 29.6% (8/27) of participants reported a total of 31 adverse events considered related to sapropterin treatment. Adverse events considered related to sapropterin included infections and infestation (3/27, 11.1%), gastrointestinal disorders (3/27, 11.1%) and amino acid concentrations decrease (6/27, 22.2%). Serious adverse events were reported by 3 people in the sapropterin group (11.1%, 5 events) and 1 person in the diet-only group (3.7%, 2 events). Serious adverse events in the sapropterin group included gastroenteritis, rash and stomatitis, and in the diet only group bronchiolitis and bronchopneumonia. No participants withdraw from the study due to adverse events.		

Critical appraisal summary: This is an open-label randomised controlled trial. The lack of blinding means the study is susceptible to bias and confounding. All participants were accounted for and intention-to-treat analysis used for efficacy outcomes.

Strengths of the study include long follow-up (26 weeks) and the inclusion of a number of patient-orientated outcomes. However, interpretation of results is limited by a lack of numerical results for some outcomes, with results reported diagrammatically or in a narrative form only.

[1] There is no published minimal clinically important difference for this outcome, see the Results section for a discussion on the clinical relevance of these results.

Study reference 6: Burton et al. 2015							
P1- Double-blind, randomised control trial (13 weeks) with open-label extension phase (13 weeks)	36 centres across the United States and Canada. 118 adults and children aged 8 year and over (mean age approximately 20 years, 58% male) with PKU responsive to sapropterin (defined as a blood phenylalanine concentration reduction of ≥20%). 38/118 participants (32%) had ADHD symptoms at baseline (mean age approximately 19 years, 61% male). 84% of participants with ADHD symptoms were not taking ADHD medication at baseline.	Sapropterin (dose not reported) (n=61) Placebo (n=57) Participants were required to continue on their current diet. The authors do not provide details on the diets the participants followed, although at baseline the mean phenylalanine levels were 680 micromol/litre in the sapropterin group and 790 micromol/litre in the placebo group. These are above the recommended upper limits, which suggests at least some people in the study were not following a strict phenylalanine-restricted diet.	Primary Clinical effectiveness	Change in ADHD symptoms at 13 weeks Measured in children by change in total score on the ADHD Rating Scale (ADHD RS, completed by parents of participants). Measured in adults by change in ADHD Self-Report Scale (ASRS).	Results reported for the sub-group of participants who were responsive to sapropterin and had ADHD symptoms at baseline (n=38). At week 13, participants in the sapropterin group had a change in ADHD RS/ASRS Total Score of −9.1 points (from a baseline score of 28.9) and participants in the placebo group a change of −4.9 points (from a baseline score of 31.2). No statistically significant difference between groups (between group difference −4.2, 95% CI −8.9 to 0.6, p=0.085). There was also no significant difference between groups in the ADHD RS/ASRS hyperactivity/impulsivity subscale score (−1.0, 95% CI −3.4 to 1.4, p=0.396). However, a statistically significance difference in favour of sapropterin was observed for the ADHD RS/ASRS inattention subscale score at 13 weeks (−3.4, 95% CI −6.6 to −0.2, p=0.036).	7/10	Direct study focusing on people with the indication and characteristics of interest
			Primary Clinical effectiveness	Change in global function at week 13 Proportion of participants with a Clinical Global Impression of Improvement (CGI-I) scale rating of 1 (very much improved) or 2 (much improved).	In the sapropterin group, 21.7% of participants were much improved or very much improved in CGI-I scale, compared with 26.3% in the placebo group. No statistically significant difference between treatment groups (relative risk ratio 0.87, 95% CI 0.46 to 1.64, p=0.670).		

			Secondary Clinical effectiveness	Executive function at week 13 Measured by the Global Executive Composite and Index scores from the Behaviour Rating Inventory of Executive Function (BRIEF), reported as stand T-score.	Results reported separately for participants aged <18 years and ≥18 years. **Global Executive Composite (GEC)** <u>Children and young people (<18 years)</u> At week 13, participants aged <18 years in the sapropterin group had a change in GEC score of −4.8 (from 63.9 at baseline), compared with −0.7 (from 63.7 at baseline) in the placebo group. Statistically significant difference between groups of −4.1 (95% CI −7.9 to −0.3, p=0.034). <u>Adults (≥18 years)</u> At week 13, adults treated with sapropterin had a change in GEC score of −9.1 points (from 55.4 at baseline), compared with −8.1 points (from 59.2 at baseline) in the placebo group. No statistically significant difference between groups (−1.0, 95% CI −5.5 to 3.6, p=0.661). **Metacognition Index (MI)** <u>Children and young people (<18 years)</u> At week 13, people <18 years in sapropterin group had a change in MI score of −4.1 (from 64.9 at baseline) compared with +0.3 (from 66.6 at baseline) in the placebo group. Statistically significant between group difference of −4.4 (95% CI −8.5 to −0.2, p=0.038). <u>Adults (≥18 years)</u>		

					No statistically significant difference at week 13 between sapropterin (−7.9 points from 54.2 at baseline) and placebo (−7.3 points from 60.2 at baseline). Between group difference of −0.5, 95% CI −5.3 to 4.2, p=0.824. **Behaviour Regulation Index (BRI)** <u>Children and young poeple (<18 years)</u> Participants aged <18 years treated with sapropterin had a mean change of −4.3 (from 59.6 at baseline) compared with −0.9 (from 56.9 at baseline) for people treated with placebo. The difference between groups was not statistically significant (treatment difference −3.4, 95% CI −6.8 to 0.0, p=0.053). <u>Adults (≥18 years)</u> In adults there was no statistically significant difference in BRI score between sapropterin (−8.9 from 56.3 at baseline) compared with placebo (−7.2 from 56.3 at baseline), between group difference of −1.7 (95% CI −5.8 to 2.3, p=0.396).		
			Secondary Safety	Adverse events	The most frequently reported adverse events in the sapropterin group during the 13 week double-blind phase were headache (25.5%), nasopharyngitis (11.2%) and diarrhoea (10.2%). Across the total 26 week study period, most adverse events		

					were mild or moderate in severity (95%). One adverse event led to a patient withdrawing from the study, a case of increased heart-rate, considered possibly or probably due to treatment with sapropterin.		
Critical appraisal summary: This is a multicentre, double-blind, randomised controlled trial. Randomisation methods are partially described by the authors and it is not clear whether allocation was concealed. Some important element so of the study design are not described in detail, for example, the dose of sapropterin used. All participants are accounted for, and intention-to-treat analysis was carried out. Power calculations are reported for the primary outcomes, although the study would appear to be under-powered for the ADHD outcome. Some outcomes are only report by age sub-group, further reducing the power of the study. Baseline characteristics were comparable across treatment arms. Although the study include a 13 week double-blind phase and a 13 week open-label phase, the majority of efficacy outcomes are reported only of the double-blind phase. A major strength of the study is the focus on patient-orientated outcomes not reported in older RCTs.							
Study reference 7: Longo et al. 2015							
P1- Open-label, propective, uncontrolled study	Multicentre study 65 children aged 0 to 6 years at screening with PKU / HPA responsive to sapropterin and who had at least 2 blood phenylalanine concentrations ≥360 micromol/ litre taken at least 3 days apart. The mean age at enrolment was 3.14 years and 36.4% were male. The baseline blood phenylalanine level was 331.2 micromol/ litre. 65 children remained in the study until the 6 month evaluation. 55 children remained in the study until the 2 year evaluation. Participants were considered 'per-protocol' responders if they had a ≥30% reduction in mean blood phenylalanine concentration (n=63) or 'clinical' responders if they had	Sapropterin 20 mg/kg/day. Dose reductions were permitted after week 5 for children who did not tolerate this dose. (n=65) No control All participants had a phenylalanine-restricted diet during the study, designed to keep phenylalanine within recommended limits.	Primary Clinical effectiveness	Change in neurocognitive function from baseline to 2 years, measured using: The Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III) every 6 months for children aged 0 to 29 months. The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) every 12 months for children aged 30 months to 6 years. The Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) every 2 years for children aged 7 years and over.	At baseline the average Full Scale Intelligence Quotient (FSIQ) score was not significantly different from the population norm of 100. In total, 25 children had baseline and 2-year WPPSI-III and WISC-IV scores. There was no statistically significant change in FSIQ score from baseline (103±12) compared with 2-year follow-up (104±10, p=0.50). Mean scores on the Bayley-III score from baseline to year 2 were also maintained within the normative range of 100±1, with no significant change over time. Numerical results not reported. The authors report that after starting sapropterin, no infant or toddler received a score less than 85 on the Bayley-III cognitive composite index.	5/10	Direct study focusing on people with the indication and characteristics of interest

	a <30% reduction in mean phenylalanine concentration but maintained blood phenylalanine within target range (120 to 360 micromol/ litre) despite dietary phenylalanine intake (n=8).		Secondary Clinical effectiveness	Blood phenylalanine levels	At baseline, phenylalanine levels were ≤240 micromol/ litre in 18/55 (33%) children. This increased to 35/52 (67%) at 6 months, remaining at 32/50 (64%) at 2 years.		
			Secondary Clinical effectiveness	Growth parameters- height, weight and head circumference	Mean baseline z-scores for height (0.4±0.9), weight (0.4±0.8) and head circumference (0.3±1.0) were slightly above the 50th percentile for the 2000 Centers for Disease Control and Prevention reference values. These values were maintained throughout the 2-year follow-up, with no statistically significant change from baseline.		
			Secondary Safety	Adverse events	Adverse events considered possibly or probably related to sapropterin included vomiting (12.7%), diarrhoea (10.9%), upper respiratory tract infection (10.9%), abdominal pain (9.1%) and nasal congestion (9.1%). 6 serious adverse events occurred, none of which were considered related to sapropterin.		
Critical appraisal summary: This is a prospective, observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. There was no control group and outcomes are limited to comparisons of baseline to study end (2 years). This publication reports on a 2-year interim analysis of a 7-year study. The study appears to have a high drop-out rate between the 6-month and 2-year follow-up which the authors do not explain. Full numerical results are not reported for all outcomes, making interpretation and analysis difficult. The strength of this study is the inclusion of patient-orientated outcome, and this is the only included study to report on neurocognitive functioning / intelligence.							
Reference study 8: Aldámiz-Echevarría et al. 2015							

P1- Retrospective longitudinal study	Conducted across 14 Spanish hospitals 22 children (0 to 4 years) with PKU responsive to sapropterin. 44 children treated with phenylalanine-restricted diet alone.	22 received sapropterin (or [6R]-L-erythro-5,6,7,8-tetrahydrobiopterin before 2009) (n=22) Results are also reported for 44 children treated with low phenylalanine diet alone (n=44) Patients were followed up every 6 months. All participants were required to have good adherence to their prescribed diet, although the authors do not provide details on the diets of people taking sapropterin, and the degree of phenylalanine restriction. Over the course of the study, people treated with sapropterin gradually increased their intake of natural protein and reduced intake of amino acid supplements.	Clinical effectiveness	Physical growth parameters from baseline to 1 year	No statistically significant difference in any growth parameter between the sapropterin and diet-only groups, and from baseline to 6- or 12-months within either group. **Weight Z-score** Sapropterin: baseline= −0.24, 12 months= −0.19, p=0.552 Diet only: baseline= −0.33, 12 months= −0.48, p>0.05 **Height Z-score** Sapropterin: baseline= −0.57, 12 months= −0.52, p=0.887 Diet only: baseline= −0.92, 12 months=0.78, p>0.05 **BMI Z-score** Sapropterin: baseline= 0.17, 12 months= 0.18, p=0.421 Diet only: baseline= 0.17, 12 months= −0.07, p>0.05 **Growth rate Z-score** Sapropterin: baseline= 0.96, 12 months= 0.90, p= 0.433 Diet only: baseline= 1.21, 12 months= 1.26, p>0.05	5/10	Direct study focusing on people with the indication and characteristics of interest.

Critical appraisal summary: This is a retrospective, longitudinal study, which is susceptible to bias, confounding and other methodological problems. Outcome assessments were not blinded. A group of patients managed on diet alone were observed and comparisons made with this group. Although the study is of low quality, the authors report detailed results for each group of patients, including some statistical analysis. It should be noted that a study from the same research group published 2 years earlier is also included in this evidence review. It is not clear from the publications whether there is any overlap in study populations between the 2 studies, and it is possible that some patients were included in both studies.							
Reference study 9: Aldámiz-Echevarría et al. 2013							
P1- Retrospective longitudinal study	13 centres in Spain 38 children and young people aged ≤16 years with PKU responsive to sapropterin	Sapropterin (or [6R]-L-erythro-5,6,7,8-tetrahydrobiopterin before 2009) (n=38) Diet alone (n=76) All participants were required to be on a phenylalanine-restricted diet. Over the course of the study, people treated with sapropterin gradually increased their intake of natural protein and reduced intake of amino acid supplements.	Clinical effectiveness	Physical growth parameters (height, weight, BMI and growth rate) at 2 year follow-up	36 children treated with sapropterin and 72 children managed using diet only were followed up at 2 years. In the sapropterin group, 10/36 (28%) were managed on sapropterin alone and ate normal diets. There was no statistically significant difference from baseline to year 2 in mean Z-score for any of the growth parameters for patients treated with either sapropterin or diet alone. **Weight Z-score** Sapropterin: baseline= −0.16, year 2= −0.75, p=0.33 Diet only: baseline= −0.55, year 2= −0.52, p=0.71 **Height Z-score** Sapropterin: baseline= −0.71, year 2= −0.73, p=0.59 Diet only: baseline= −0.76, year 2= −0.90, p=0.53 **BMI Z-score** Sapropterin: baseline= 0.31, year 2= 0.37, p=0.63 Diet only: baseline= −0.17, year 2= −0.12, p=0.30 **Growth rate (GR) Z-score**	5/10	Direct study focusing on people with the indication and characteristics of interest.

					Sapropterin: baseline= 0.15, year 2= 0.05, p=0.14 Diet only: baseline= 0.02, year 2=0.10, p=0.72		
			Clinical effectiveness	Physical growth parameters (height, weight, BMI and growth rate) at 5 year follow-up	10 children treated with sapropterin and 20 children managed with diet only were followed up at 5 years. The authors do not report how many children treated with sapropterin could eat normal diets. There was no statistically significant difference from baseline to year 5 in mean Z-score for any of the growth parameters for patients treated with either sapropterin or diet alone. **Weight Z-score** Sapropterin: baseline= −0.08, year 5= −0.10, p=0.89 Diet only: baseline= −0.01, year 5= −0.18, p=0.13 **Height Z-score** Sapropterin: baseline= −0.29, year 5= −0.52, p=0.28 Diet only: baseline= −0.27, year 5= −0.56, p=0.08 **BMI Z-score** Sapropterin: baseline= 0.23, year 5= 0.12, p=0.54 Diet only: baseline= 0.42, year 5= 0.04, p=0.14 **Growth rate (GR) Z-score** Sapropterin: baseline= 1.62, year 5= 0.41, p=0.60		

					Diet only: baseline= 0.78, year 5= 0.34, p=0.91		
Critical appraisal summary: This is a retrospective, longitudinal study, which is susceptible to bias, confounding and other methodological problems. Outcome assessments were not blinded. A group of patients managed on diet alone were observed and comparisons made with this group. There was a considerable drop in patient numbers between the 2 and 5 years follow-up, which is not fully explained by the authors. Although the study is of low quality, the authors report detailed results for each group of patients, including some statistical analysis. It should be noted that a study from the same research group published 2 years later is also included in this evidence review. It is not clear from the publications whether there is any overlap in study populations between the 2 studies, and it is possible that some patients were included in both studies.							
Reference study 10: Feldmann et al. 2017							
P1- Prospective cohort study	Single centre in Germany. 112 adults and children (aged ≥6 years) with PKU (pre-treatment blood phenylalanine ≥360 micromol/ litre). Participants were considered sapropterin responders if they had ≥30% reduction in blood phenylalanine level following 2 weeks of sapropterin. 41.1% (46/112, 24 children) of participants responded to sapropterin and continued treatment. Participants who did not respond to sapropterin (66/112, 58.9%) remained in the study on diet alone, acting as controls.	Sapropterin 20 mg/kg/day (n=46) Diet only (n=66, participants had failed to respond to sapropterin) For people taking sapropterin, dietary phenylalanine was increased over 6 weeks through the addition of natural protein.	Clinical effectiveness	Health-related quality of life from baseline to 6 months Assessed using the KINDL^{R} questionnaire (Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern und Jugendlichen; in English: Questionnaire to assess the health-related quality of life of children and adolescents). The KINDL^{R} questionnaire covers 6 separate parameters (physical state, psychological well-being, self-esteem, family, friends and school) and total score.	The KINDL^{R} questionnaire was successfully completed at baseline and 6 months by 38 children and young people (20 in the sapropterin group and 18 in the control group). After 6 months treatment, there was no statistically significant difference between the sapropterin group and the control group for total KINDL^{R} score or any of the individual parameters. In the sapropterin group, the KINDL^{R} total score was 74.5 at baseline and 75.3 at 6 months. In the control group, the KINDL^{R} total score was 74.9 at baseline and 76.6 at 6 months (p=0.737 between groups at 6 months). These results were supported by the 49 parents who completed the KINDL^{R} questionnaire (24 in the sapropterin group and 25 in the control group), which found no significant difference between groups for the individual parameters and total KINDL^{R} score.	5/10	Direct study focusing on people with the indication and characteristics of interest.

			Clinical effectiveness	Health-related quality of life in parents Assessed using the Ulm Quality of Life Inventory for Parents (ULQIE) questionnaire. The ULQIE questionnaire covers 5 separate parameters (physical & daily functioning, satisfaction with the support from the family, emotional stability, self-development and well-being)	The ULQIE questionnaire was completed by 49 parents (24 in the sapropterin group and 25 in the control group). At 6 months, there was no significant difference in total ULQIE score between parents of children in the sapropterin group (83.9 points) compared with the control group (78.7 points, p=0.158). There was no significant difference in the individual parameters, except for emotional stability, which was significantly higher in the sapropterin group compared with the control group at 6 months (11.6 and 10.2 points respectively, p=0.037).		
			Clinical effectiveness	Phenylalanine tolerance	In people treated with sapropterin, mean phenylalanine intake was 13.8 mg/kg at baseline, increasing to 35.2 mg/kg after 6 weeks treatment with sapropterin. Changes in phenylalanine tolerance not reported for sapropterin non-responders treated with diet alone.		
Critical appraisal summary: This is a prospective cohort study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. A group of sapropterin non-responders managed by diet alone were included in the study and used as a comparator group, although non-responders are an inherently different population. Study participants were all drawn from a single centre in Germany, limiting the generalisability of the results.							
Reference study 11: Cazzorla et al. 2014							
P1- Prospective observational study	2 centres in Italy 43 people with PKU. 22 participants had mild PKU (blood phenylalanine 600 to 1,200 micromol/ litre) responsive to sapropterin, and	Sapropterin 10 mg/kg/day (mild PKU) (n=22) Diet alone (classical PKU) (n=21) The authors did not report on the diets of the participants taking	Exploratory Clinical effectiveness	Quality of life, measured using: The Pediatric Quality of Life Inventory (PedsQL) in children (6 to 16 years) The World Health Organisation QoL score	The authors state that there was no significant difference in patients or parents perception of quality of life compared with normative children's data. In children, the mean quality of life score was significantly	5/10	Direct study focusing on people with the indication and characteristics of interest

	were treated with sapropterin. Mean age 15.4 years. 21 participants had classical PKU (blood phenylalanine >1,200 micromol/ litre) and were treated with diet alone. Mean age 18.9 years.	sapropterin. The authors state that people treated with sapropterin were allowed 'relevant relaxation of the dietary-restriction', although more details are not provided.		(WHOQOL-100) in adults (≥18 years) Treatment duration varied between patients (range 1 to 11 years)	higher in the sapropterin group (mild PKU) compared with the diet alone group (classical PKU, regression coefficient 15.12, 95% CI 3.08 to 27.15, p=0.02). Mean quality of life scores were also significantly higher in adults with mild PKU treated with sapropterin compared with adults with classical PKU managed by diet alone (regression coefficient 7.89, 95% CI 2.47 to 13.31, p=0.01). Note- actual quality of life scores are not reported in the paper.		
Critical appraisal summary: This is a prospective observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. Comparison between sapropterin and diet alone is limited by the different populations receiving each intervention (mild PKU and classical PKU respectively). The authors do not report numerical results for the main study outcome, reporting differences between groups as regression coefficient only. Study participants were all drawn from 2 centres in Italy, limiting the generalisability of the results.							

8. Grade of evidence table

Use of sapropterin compared with diet only (with or without placebo) to treat phenylketonuria (PKU)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Blood phenylalanine concentration	Levy et al. 2007	7/10	Direct study	A	This outcome looked at how much phenylalanine is in a person's blood. Raised phenylalanine levels are thought to result in neurotoxicity. The studies found that people treated with sapropterin for up to 22 weeks had a reduction in blood phenylalanine concentrations of approximately 200 micromol/litre from baseline. This reduction is significantly higher than seen in people treated with placebo, whose phenylalanine levels remained the approximately the same after 6 weeks treatment. These studies suggest that sapropterin significantly reduces phenylalanine blood concentration. Care should be taken when interpreting the results of biochemical outcomes, as changes to a blood test may not translate to benefits in more patient orientated outcomes, for example, cognitive functioning.
	Lee et al. 2008	7/10	Direct study		

Use of sapropterin compared with diet only (with or without placebo) to treat phenylketonuria (PKU)					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Phenylalanine tolerance	Trefz et al. 2009	7/10	Direct study	A	This outcome looks at how much phenylalanine (from diet and supplements) a person with PKU can tolerate whilst keeping their blood phenylalanine levels within a predefined range (<360 micromol/litre). The studies found that people treated with sapropterin for 10 to 26 weeks could tolerate approximately 20-30 mg/kg more phenylalanine each day compared with people on phenylalanine restricted diet alone. These studies suggest that sapropterin significantly increases the amount of phenylalanine a person with PKU can consume each day and still keep their phenylalanine blood levels within acceptable limits. An increased phenylalanine tolerance could in theory allow a person with PKU to have a more relaxed diet containing more natural protein. However the actual benefit of increased tolerance to patients can only be determined using patient-orientated outcomes, for example, physical growth.
	Muntau et al. 2017	7/10	Direct study		
Physical growth	Muntau et al. 2017	7/10	Direct study	B	This outcome looks at how fast children with PKU grew when treated with sapropterin. A number of parameters were measured for growth, including weight, height and head circumference. Most studies reported growth using Z-scores (standard score), which report how many standard deviations from the mean a measurement sits. A Z-score of 0 is equal to the mean, or the 50th percentile for growth. A Z-score of −1 is equal to 1 standard deviation below the mean, and a Z-score of +1 is equal to 1 standard deviation above the mean. No statistically significant changes in growth were observed in any study. In Muntau et al. 2017 there was no significant difference between sapropterin and diet alone for any growth parameter, with children in both treatment arms having stable growth parameters. Longo et al. 2015 found that, at baseline children had Z-scores slightly above the 50th percentile for height, weight and head circumference (0.4, 0.4 and 0.3 respectively). These values were maintained over the 2 year follow-up, with no statistically significant difference from baseline to 2 years. Two studies by Aldámiz-Echevarría et al. (2015 and 2013) found no difference from baseline to study end (12 months and up to 5 years) for any growth parameter Z-score for either the sapropterin or the diet only group. These results suggest that sapropterin did not significantly increase physical growth compared with diet alone, despite children treated with sapropterin having a larger intake of natural protein.
	Longo et al. 2015	5/10	Direct study		
	Aldámiz-Echevarría et al. 2015	5/10	Direct study		
	Aldámiz-Echevarría et al. 2013	5/10	Direct study		

Attention deficit and hyperactivity disorder (ADHD) symptoms	Burton et al. 2015	7/10	Direct study	B	This outcome looks at symptoms of ADHD in adults and children with PKU. Symptoms were measured using the ADHD Rating Scale (ADHD RS) in children and the Adult Self-Report Scale (ASRS) in adults. 38 children and adults with PKU had ADHD symptoms at baseline. After 13 weeks treatment there was no significant difference in change from baseline in ADHD RS/ASRS Total Score for sapropterin compared with placebo (between group difference −4.2, 95% CI −8.9 to 0.6, p=0.085). Analysis of the ADHD RS/ASRS subscales-hyperactivity/impulsivity and inattention found no significant difference between treatments in the hyperactivity/impulsivity subscale (between group difference −1.0, 95% CI −3.4 to 1.4, p=0.396), and a significant difference in favour of sapropterin in the inattention subscale (between group difference −3.4, 95% CI −6.6 to −0.2, p=0.036). These results suggest that sapropterin does not improve overall ADHD symptoms compared with diet alone. Inattention symptoms of ADHD may be improved by sapropterin, although care should be taken when interpreting the positive benefits of secondary outcomes in studies that failed to demonstrate a significant result for the primary outcome.
Executive function	Burton et al. 2015	7/10	Direct study	B	This outcome looks at executive functions, a set of cognitive processes that control behaviour, and are needed for basic cognitive processes including paying attention, planning/organisation and managing tasks. Impaired executive function has been reported in people with PKU. Executive function was measured using the Global Executive Composite (GEC), Metacognition Index (MI) and Behaviour Regulation Index (BRI) scores from the Behaviour Rating Inventory of Executive Function (BRIEF). Scores for each BRIEF domain were reported as standard T-scores, and were compared to normative tables that provide T-scores, percentiles and 90% CIs by age and gender. Standard T-scores have a mean of 50 points. Higher T-scores indicate poorer executive function, with T-scores >65 typically considered clinically significant, but T-scores >60 on BRIEF self-reports may warrant clinical interpretation. There was no significant difference in any measure of executive function for adults treated with sapropterin compared with placebo. Children and young people treated with sapropterin had significantly improved GEC (treatment difference −4.1, 95% CI −7.9 to −0.3, p=0.034) and MI (treatment difference −4.4, 95% CI −8.5 to −0.2, p=0.038) scores compared with placebo. An improvement in BRI score was also observed in children and adolescents, however difference between sapropterin and placebo was not statistically significant (−3.4, 95% CI −6.8 to 0.0, p=0.053) These results suggest that children and young people treated with sapropterin may have improvements in elements of executive function. The authors note that improvements were driven by better scores on the MI scale, which includes initiation, working memory, planning/organising, organizing materials, and monitoring. The results also suggest that initiating sapropterin therapy in adults is unlikely to improve executive function. These results should be interpreted with caution as the double-blind phase of the trial was short (13 weeks), and the long-term effect of sapropterin on executive function is not known. It is also not clear why the results are reported separately by age group (rather than for the whole study population). Splitting the study population does not appear to be a predefined part of the outcome, and also reduces the power.

Neuro-cognitive function / Intelligence	Longo et al. 2015	5/10	Direct study	C	This outcome looked at neuro-cognitive functioning / intelligence in children with PKU, reported as Full Scale Intelligence Quotient (FSIQ) score. The scoring tool used was dependent on the age of the child. The study reported that at baseline the average FSIQ score was not significantly different to the population average of 100 (numerical results not reported). Over the 2 year follow-up there was no significant change in FSIQ score, leading the authors to conclude that sapropterin preserved neurocognitive function. These results suggest that children treated with sapropterin for 2 years did not have a statistically significant reduction in neuro-cognitive function. These results should be interpreted with caution, since there was no control group it is not clear whether people treated with diet alone would have a significant reduction in neuro-cognitive function during the 2 year study period. The study is further limited by the authors not reporting numerical results for all neuro-cognitive scoring tools.
Neuro-motor development	Muntau et al. 2017	7/10	Direct study	B	This outcome looked at neuro-motor development, covering 4 developmental milestones: personal-social function, language, fine motor skills and gross motor skills. At week 26 there was no significant difference between sapropterin and diet only for any of the developmental milestones. Results only presented diagrammatically. These results suggest that sapropterin does not improve neuro-motor development compared with diet alone. These results should be interpreted with caution as the study only had a 6 month follow-up period, the longer term effects on development are not reported. It is also not clear from the published paper how the individual developmental milestones were assessed, and whether validated methods were used.
Global function	Burton et al. 2015	7/10	Direct study	B	This outcome looks at global functioning, assessed using the Clinical Global Impression of Improvement (CGI-I) scale. The CGI-I scale involves a person's clinician scoring how much their condition has changed from baseline. The scale is scored from 1 (very much improved) to 7 (very much worse). There was no significant difference in the proportion of people 'much improved' (score 2) or 'very much improved' (score 1) in the sapropterin group (21.7%) compared with the placebo group (26.3%, p=0.670). These results suggest that sapropterin does not improve global function (as assessed by a clinician) compared with placebo. These results should be interpreted with caution as the double-blind phase of the trial was short (13 weeks), and the long-term effect of sapropterin on global function is not known.
Health-related quality of life	Feldmann et al. 2017	5/10	Direct study	B	This outcome looked at the impact of sapropterin treatment on quality of life. Both studies investigated patient quality of life, with Feldmann et al. (2017) also reporting on parent quality of life. Different scoring tools were used to assess quality of life. The studies report conflicting results, with no improvements in quality of life observed for children with PKU or their parents in the study by Feldmann et al. In Cazzorla et al., people with mild PKU treated with sapropterin reported significantly better quality of life compared with people with classical PKU treated with diet alone.
	Cazzorla et al. 2014	5/10	Direct study		

					It is not clear whether sapropterin improves quality of life in children and adults with PKU.
Adverse events	Levy et al. 2007	7/10	Direct study	A	This outcome looked at the number of people reporting adverse events (side effects) while taking sapropterin. Across the 6 studies the incidence of reported adverse events was high, although the majority of events were mild or moderate in severity, and few people withdrew from studies due to adverse events. The most frequently reported adverse events in the clinical trials included upper respiratory tract infections, headache, vomiting, rhinorrhoea, upper abdominal pain, dizziness, diarrhoea and pyrexia.
	Trefz et al. 2009	8/10	Direct study		
	Burton et al. 2015	8/10	Direct study		
	Muntau et al. 2017	7/10	Direct study		
	Lee et al. 2008	7/10	Direct study		
	Burton et al. 2011	8/10	Direct study		
	Longo et al. 2015	5/10	Direct study		

9. Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients with PKU who are not pregnant

I – Intervention Which intervention, treatment or approach should be used?	Sapropterin
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Dietary control without sapropterin
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* Halt disease progression and maintain good quality of life measured through; • Improvements in phenylalanine control • Prevention of loss of IQ function *Important to decision-making:* • Improvement in cognitive profile (e.g. executive functions). • Increase in dietary protein intake • Quality of life • Long term outcomes (neuro-psychiatric outcomes in adults) • Adverse effects • Cost effectiveness
Assumptions / limits applied to search	
Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc. • Study designs: systematic reviews, randomised controlled trials, comparative studies and case series (n>5) • Non-English language studies will be excluded. • Letters and other non-peer reviewed publications will not be included. • Papers published longer than 20 years ago will be excluded.	

10. Search strategy

Database search strategies

Database: Medline

Platform: Ovid

Version: <1946 to July 17, 2018>

Search date: 18/7/18

Number of results retrieved: 349

Search strategy:

1 sapropterin.ti,ab. (94)

2 tetrahydrobiopterin.ti,ab. (2994)

3 bh4.ti,ab. (1511)

4 thb.ti,ab. (587)

5 kuvan.ti,ab. (19)

6 phenoptin.ti,ab. (2)

7 or/1-6 (4021)

8 Phenylketonuria*.ti,ab. (5039)

9 PKU.ti,ab. (2353)

10 "folling* disease".ti,ab. (33)

11 ((pah or "phenylalanine hydroxylase") adj2 deficien*).ti,ab. (299)

12 "oligophrenia phenylpyruvica".ti,ab. (9)

13 hyperphenylalaninaemia.ti,ab. (263)

14 Phenylketonurias/ (6548)

15 or/8-14 (7533)

16 7 and 15 (550)

17 limit 16 to english language (503)

18 limit 17 to yr="1998 -Current" (390)

19 limit 18 to (letter or historical article or comment or editorial or news) (18)

20 18 not 19 (372)

21 animals/ not humans/ (4441716)

22 20 not 21 (351)

23 remove duplicates from 22 (349)

Database: Medline in-process

Platform: Ovid

Version: <July 17, 2018>

Search date: 18/7/18

Number of results retrieved: 41

Search strategy:

1 sapropterin.ti,ab. (16)

2 tetrahydrobiopterin.ti,ab. (124)

3 bh4.ti,ab. (323)nct

4 thb.ti,ab. (83)

5 kuvan.ti,ab. (4)

6 phenoptin.ti,ab. (0)

7 or/1-6 (467)

8 Phenylketonuria*.ti,ab. (279)

9 PKU.ti,ab. (212)

10 "folling* disease".ti,ab. (0)

11 ((pah or "phenylalanine hydroxylase") adj2 deficien*).ti,ab. (25)

12 "oligophrenia phenylpyruvica".ti,ab. (0)

13 hyperphenylalaninaemia.ti,ab. (5)

14 Phenylketonurias/ (0)

15 or/8-14 (326)

16 7 and 15 (41)

17 limit 16 to english language (41)

18 limit 17 to yr="1998 -Current" (41)

Database: Medline epubs ahead of print

Platform: Ovid

Version: <July 17, 2018>

Search date: 18/7/18

Number of results retrieved: 9

Search strategy:

1 sapropterin.ti,ab. (6)

2 tetrahydrobiopterin.ti,ab. (26)

3 bh4.ti,ab. (32)

4 thb.ti,ab. (12)

5 kuvan.ti,ab. (2)

6 phenoptin.ti,ab. (1)

7 or/1-6 (55)

8 Phenylketonuria*.ti,ab. (48)

9 PKU.ti,ab. (33)

10 "folling* disease".ti,ab. (0)

11 ((pah or "phenylalanine hydroxylase") adj2 deficien*).ti,ab. (3)

12 "oligophrenia phenylpyruvica".ti,ab. (0)

13 hyperphenylalaninaemia.ti,ab. (1)

14 Phenylketonurias/ (0)

15 or/8-14 (52)

16 7 and 15 (10)

17 limit 16 to english language (10)

18 limit 17 to yr="1998 -Current" (9)

Database: Medline daily update

Platform: Ovid

Version: <July 17, 2018>

Search date: 18/7/18

Number of results retrieved: 1

Search strategy:

1 sapropterin.ti,ab. (0)

2 tetrahydrobiopterin.ti,ab. (1)

3 bh4.ti,ab. (2)

4 thb.ti,ab. (2)

5 kuvan.ti,ab. (0)

6 phenoptin.ti,ab. (0)

7 or/1-6 (4)

8 Phenylketonuria*.ti,ab. (2)

9 PKU.ti,ab. (0)

10 "folling* disease".ti,ab. (0)

11 ((pah or "phenylalanine hydroxylase") adj2 deficien*).ti,ab. (0)

12 "oligophrenia phenylpyruvica".ti,ab. (0)

13 hyperphenylalaninaemia.ti,ab. (0)

14 Phenylketonurias/ (1)

15 or/8-14 (2)

16 7 and 15 (1)

17 limit 16 to english language (1)

18 limit 17 to yr="1998 -Current" (1)

Database: Embase

Platform: Ovid

Version: <1974 to 2018 July 17>

Search date: 18/7/18

Number of results retrieved: 414

Search strategy:

1 sapropterin.ti,ab. (258)

2 tetrahydrobiopterin.ti,ab. (4150)

3 bh4.ti,ab. (3034)

4 thb.ti,ab. (924)

5 kuvan.ti,ab. (91)

6 phenoptin.ti,ab. (2)

7 sapropterin/ (503)

8 or/1-7 (6219)

9 Phenylketonuria*.ti,ab. (6644)

10 PKU.ti,ab. (3862)

11 "folling* disease".ti,ab. (25)

12 ((pah or "phenylalanine hydroxylase") adj2 deficien*).ti,ab. (462)

13 "oligophrenia phenylpyruvica".ti,ab. (3)

14 hyperphenylalaninaemia.ti,ab. (321)

15 phenylketonuria/ (9036)

16 or/9-15 (10108)

17 8 and 16 (962)

18 limit 17 to english language (895)

19 limit 18 to yr="1998 -Current" (778)

20 19 not (letter or editorial).pt. (762)

21 20 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (455)

22 nonhuman/ not human/ (4196047)

23 21 not 22 (426)

24 remove duplicates from 23 (414)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – Issue 7 of 12, July 2018

DARE – Issue 2 of 4, April 2015

CENTRAL – Issue 6 of 12, June 2018

HTA – Issue 4 of 4, October 2016

NHS EED – Issue 2 of 4, April 2015

Search date:

Number of results retrieved: CDSR – 1; DARE – 1; CENTRAL – 36; HTA – 1; NHS EED - 0

Search strategy:

#1 sapropterin:ti,ab 38

#2 tetrahydrobiopterin:ti,ab 91

#3 bh4:ti,ab 64

#4 thb:ti,ab 52

#5 kuvan:ti,ab 12

#6 phenoptin:ti,ab 0

#7 {or #1-#6} 180

#8 Phenylketonuria*:ti,ab 239

#9 PKU:ti,ab 199

#10 "folling* disease":ti,ab 0

#11 ((pah or "phenylalanine hydroxylase") near/2 deficien*):ti,ab 9

#12 "oligophrenia phenylpyruvica":ti,ab 0

#13 hyperphenylalaninaemia:ti,ab 12

#14 [mh Phenylketonurias] 129

#15 {or #8-#14} 315

#16 #7 and #15 Publication Year from 1998 to 2018 39

11. Evidence selection

A literature search was conducted which identified 519 references (see search strategy for full details). These references were screened using their titles and abstracts and 39 references were obtained and assessed for relevance. Of these, 11 references are included in the evidence summary. The remaining 28 references were excluded and are listed in the following table.

Study reference	Reason for exclusion
Burlina A and Blau N (2009) Effect of BH(4) supplementation on phenylalanine tolerance. Journal of inherited metabolic disease 32(1), 40–5	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance reported in higher quality studies
Burton BK, Bausell H, Katz R et al. (2010) Sapropterin therapy increases stability of blood phenylalanine levels in patients with BH4-responsive phenylketonuria (PKU). Molecular genetics and metabolism 101(2-3), 110–4	Study not prioritised (not the best available evidence) Data on mean phenylalanine concentrations reported in higher quality studies
Christ SE, Moffitt AJ, Peck D et al. (2013) The effects of tetrahydrobiopterin (BH4) treatment on brain function in individuals with phenylketonuria. NeuroImage. Clinical 3, 539–47	Study not prioritised (not the best available evidence) Data on cognitive function reported in higher quality studies
Couce ML, Boveda MD, Valerio E et al. (2012) Long-term pharmacological management of phenylketonuria, including patients below the age of 4 years. JIMD reports 2, 91–6	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance reported in higher quality studies

Demirdas S, Maurice-Stam H, Boelen Carolien CA et al. (2013) Evaluation of quality of life in PKU before and after introducing tetrahydrobiopterin (BH4); a prospective multi-center cohort study. Molecular genetics and metabolism 110 Suppl, S49–56	Study not prioritised (not the best available evidence) Data on quality of life reported in higher quality studies
Douglas TD, Ramakrishnan U, Kable JA et al. (2013) Longitudinal quality of life analysis in a phenylketonuria cohort provided sapropterin dihydrochloride. Health and Quality of Life Outcomes 11, 218	Study not prioritised (not the best available evidence) Data on quality of life reported in higher quality studies
Gokmen OH, Lammardo AM, Motzfeldt K et al. (2013) Use of sapropterin in the management of phenylketonuria: seven case reports. Molecular genetics and metabolism 108(2), 109–11	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
Hennermann JB, Roloff S, Gebauer C et al. (2012) Long-term treatment with tetrahydrobiopterin in phenylketonuria: treatment strategies and prediction of long-term responders. Molecular genetics and metabolism 107(3), 294–301	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance reported in higher quality studies
Huijbregts SCJ, Bosch AM, Simons Quirine A, et al. (2018) The impact of metabolic control and tetrahydrobiopterin treatment on health related quality of life of patients with early-treated phenylketonuria: A PKU-COBESO study. Molecular genetics and metabolism S1096-7192(18)30274-9. doi: 10.1016/j.ymgme	Study not prioritised (not the best available evidence) Data on quality of life reported in higher quality studies
Humphrey M, Nation J, Francis I et al. (2011) Effect of tetrahydrobiopterin on Phe/Tyr ratios and variation in Phe levels in tetrahydrobiopterin responsive PKU patients. Molecular genetics and metabolism 104(1-2), 89–92	Study not prioritised (not the best available evidence) Data on mean phenylalanine concentrations reported in higher quality studies
Keil S, Anjema K, van Spronsen et al. (2013) Long-term follow-up and outcome of phenylketonuria patients on sapropterin: a retrospective study. Pediatrics 131(6), e1881–8	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance, mean phenylalanine concentrations and quality of life reported in higher quality studies
Lambruschini N, Perez-Duenas B, Vilaseca MA et al. (2005) Clinical and nutritional evaluation of phenylketonuric patients on tetrahydrobiopterin monotherapy. Molecular genetics and metabolism 86 Suppl 1, S54–60	Study not prioritised (not the best available evidence) Data on clinical outcomes reported in higher quality studies
Leuret O, Barth M, Kuster A et al. (2012) Efficacy and safety of BH4 before the age of 4 years in patients with mild phenylketonuria. Journal of inherited metabolic disease 35(6), 975–81	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
Lindegren M, Krishnaswami S, Reimschisel T et al. (2013) A Systematic Review of BH4 (Sapropterin) for the Adjuvant Treatment of Phenylketonuria. JIMD reports 8, 109–19	Systematic review – individual studies considered for inclusion

Longo N, Arnold GL, Pridjian G et al. (2015) Long-term safety and efficacy of sapropterin: the PKUDOS registry experience. Molecular genetics and metabolism 114(4), 557–63	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance reported in higher quality studies
Moseley KD, Ottina MJ, Azen CG et al (2015) Pilot study to evaluate the effects of tetrahydrobiopterin on adult individuals with phenylketonuria with measurable maladaptive behaviors. CNS spectrums 20(2), 157–63	Study not prioritised (not the best available evidence) Data on mean phenylalanine concentrations reported in higher quality studies
Scala I, Concolino D, Della C et al. (2015) Long-term follow-up of patients with phenylketonuria treated with tetrahydrobiopterin: a seven years experience. Orphanet journal of rare diseases 10, 14	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
Shintaku H and Ohura T (2014) Sapropterin is safe and effective in patients less than 4-years-old with BH4-responsive phenylalanine hydrolase deficiency. The Journal of pediatrics 165(6), 1241–4	Study not prioritised (not the best available evidence) Data on mean phenylalanine concentrations reported in higher quality studies
Singh RH, Quirk ME, Douglas TD et al. (2010) BH(4) therapy impacts the nutrition status and intake in children with phenylketonuria: 2-year follow-up. Journal of inherited metabolic disease 33(6), 689–95	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and growth reported in higher quality studies
Somaraju UR and Merrin M (2015) Sapropterin dihydrochloride for phenylketonuria. Cochrane Database of Systematic Reviews (3)	Systematic review – individual studies considered for inclusion
Tansek MZ, Groselj U, Kelvisar M et al. (2016) Long-term BH4 (sapropterin) treatment of children with hyperphenylalaninemia - effect on median Phe/Tyr ratios. Journal of pediatric endocrinology & metabolism : JPEM 29(5), 561–6	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
Thiele AG, Rohde C, Mutze U et al. (2015) The challenge of long-term tetrahydrobiopterin (BH4) therapy in phenylketonuria: Effects on metabolic control, nutritional habits and nutrient supply. Molecular genetics and metabolism reports 4, 62–7	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
Trefz FK, Muntau AC, Lagler FB et al. (2015) The Kuvan Adult Maternal Paediatric European Registry (KAMPER) Multinational Observational Study: Baseline and 1-Year Data in Phenylketonuria Patients Responsive to Sapropterin. JIMD reports 23, 35–43	Study not prioritised (not the best available evidence) Data on long-term safety reported in higher quality studies
Trefz FK, Scheible D, Frauendienst-Egger GKH et al. (2005) Long-term treatment of patients with mild and classical phenylketonuria by tetrahydrobiopterin. Molecular genetics and metabolism 86 Suppl 1, S75–80	Study not prioritised (not the best available evidence) Data on mean phenylalanine concentrations and growth reported in higher quality studies

Trefz FK, van Spronsen FJ, MacDonald A et al. (2015) Management of adult patients with phenylketonuria: survey results from 24 countries. European journal of pediatrics 174(1), 119–27	Study not prioritised (not the best available evidence) Data on long-term safety reported in higher quality studies
Unal O, Gokmen-Ozel H, Coskun T et al. (2015) Sapropterin dihydrochloride treatment in Turkish hyperphenylalaninemic patients under age four. The Turkish journal of pediatrics 57(3), 213-8	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and mean phenylalanine concentrations reported in higher quality studies
White DA, Antenor-Dorsey JV, Grange DK et al. (2013) White matter integrity and executive abilities following treatment with tetrahydrobiopterin (BH4) in individuals with phenylketonuria. Molecular genetics and metabolism 110(3), 213–7	Study not prioritised (not the best available evidence) Data on clinical outcomes reported in higher quality studies
Ziesch B, Weigel J, Thiele A, et al. (2012) Tetrahydrobiopterin (BH4) in PKU: effect on dietary treatment, metabolic control, and quality of life. Journal of inherited metabolic disease 35(6), 983–92	Study not prioritised (not the best available evidence) Data on phenylalanine tolerance and quality of life reported in higher quality studies

12. Related NICE guidance and NHS England clinical policies

NHS England has published Clinical Commissioning Policies on:

The use of Sapropterin in children with Phenylketonuria (2015)

Sapropterin for Phenylketonuria: Use in Pregnancy (2013)

A NICE Technology Appraisal has been proposed for:

Sapropterin for treating phenylketonuria (ID1475)

13. Terms used in this evidence summary

Abbreviations

Term	Definition
ADHD	Attention deficit and hyperactivity disorder
BH4	Tetrahydrobiopterin
EPAR	European Public Assessment Report
FSIQ	Full Scale Intelligence Quotient
KINDL^{R}	Fragebogen zur Erfassung der gesundheitsbezogenen Lebensqualität bei Kindern und Jugendlichen; In English: Questionnaire to assess the health-related quality of life of children and adolescents
MCID	Minimal clinically important difference
PedsQL	Pediatric Quality of Life Inventory
PKU	Phenylketonuria
PKU-QOLQ	PKU quality of life questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
SPC	Summary of Product Characteristics
ULQIE	Ulm Quality of Life Inventory for Parents
WHOQOL-100	World Health Organisation QoL score

Medical definitions

Term	Definition
Amino acid	Building blocks of protein
Hyperphenylalaninaemia	Raised phenylalanine concentration in the blood and body fluids
Phenylalanine	An essential amino acid provided by protein in the diet
Phenylalanine hydroxylase	Enzyme responsible for the conversion of phenylalanine
Phenylketonuria	An autosomal recessive genetic disorder characterised by an increase of phenylalanine in the blood and body fluids

14. References

Aldámiz-Echevarría L, Bueno MA, Couce ML et al. (2013) Tetrahydrobiopterin therapy vs phenylalanine-restricted diet: Impact on growth in PKU. Molecular genetics and metabolism 109(4), 331–8

Aldamiz-Echevarria L, Bueno MA, Couce ML et al. (2015) 6R-tetrahydrobiopterin treated PKU patients below 4 years of age: Physical outcomes, nutrition and genotype. Molecular genetics and metabolism 115(1), 10–16

Burton BK, Nowacka M, Hennermann JB et al. (2011) Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: results of a phase 3b study. Molecular genetics and metabolism 103(4), 315–22

Burton B, Grant M, Feigenbaum A et al. (2015) A randomized, placebo-controlled, double-blind study of sapropterin to treat ADHD symptoms and executive function impairment in children and adults with sapropterin-responsive phenylketonuria. Molecular genetics and metabolism 114(3), 415–24

Cazzorla C, Cegolon L, Burlina AP et al. (2014) Quality of Life (QoL) assessment in a cohort of patients with phenylketonuria. BMC Public Health 14, 1243

Feldmann R, Wolfgart E, Weglage J et al. (2017) Sapropterin treatment does not enhance the health-related quality of life of patients with phenylketonuria and their parents. Acta Paediatrica 106(6), 953–9

Lee P, Treacy EP, Crombez E et al. (2008) Safety and efficacy of 22 weeks of treatment with sapropterin dihydrochloride in patients with phenylketonuria. American Journal of Medical Genetics. 146A(22), 2851–9

Levy HL, Milanowski A, Chakrapani A et al. (2007) Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study. The Lancet 370(9586), 504–10

Longo N, Siriwardena K, Feigenbaum A et al. (2015) Long-term developmental progression in infants and young children taking sapropterin for phenylketonuria: a two-year analysis of safety and efficacy. Genetics in Medicine 17(5), 365–73

Muntau AC, Burlina A, Eyskens F et al. (2017) Efficacy, safety and population pharmacokinetics of sapropterin in PKU patients <4 years: results from the SPARK open-label, multicentre, randomized phase IIIb trial. Orphanet Journal of Rare Diseases 12(1), 47

Trefz FK, Burton BK, Longo N et al. (2009) Efficacy of sapropterin dihydrochloride in increasing phenylalanine tolerance in children with phenylketonuria: a phase III, randomized, double-blind, placebo-controlled study. The Journal of Pediatrics 154(5), 700-7

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